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Title: Tackling gaps in developing life-changing treatments for dementia

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Abstract

Since the G8 Dementia Summit in 2013, a number of initiatives have been established with the aim of facilitating the discovery of a disease-modifying treatment for dementia by 2025. This report is a summary of the findings and recommendations of a meeting titled 'Tackling gaps in developing life-changing treatments for dementia', hosted by Alzheimer's Research UK in May 2018. The aim of the meeting was to identify, review and highlight the areas in dementia research that are not currently being addressed by existing initiatives. It reflects the views of leading experts in the field of neurodegeneration research challenged with developing a strategic action plan to address these gaps and make recommendations on how to achieve the G8 Dementia Summit goals. The plan calls for significant advances in: (1) translating newly identified genetic risk factors into a better understanding of the impacted biological processes; (2) enhanced understanding of selective neuronal resilience to inform novel drug targets; (3) facilitating robust and reproducible drug target validation; (4) appropriate and evidence-based selection of appropriate subjects for proof-of-concept clinical trials; (5) improving approaches to assess drug-target engagement in humans; and (6) innovative approaches to conducting clinical trials if we are able to detect disease 10-15 years earlier than we currently do today.

Keywords: Alzheimer's disease; Dementia; Disease-modifying treatment; Earlier detection; Diagnosis; Neurodegeneration; Target validation; Clinical trials; Genetic risk factors

1. Introduction

Alzheimer's disease (AD), and other diseases that cause dementia, are the greatest health and social care challenges of our age [1]. Today, there are 50 million people living with dementia worldwide and this is projected to increase to 135 million by 2050 due to a rise in life expectancy and an ageing population [2, 3] Current therapeutics for AD can transiently improve cognitive symptoms in some patients, but they do not treat the underlying causes of dementia or slow the rate of disease progression [3, 4]. Since the success rate for the development of disease-modifying drugs for

dementia diseases has been disappointing, such as the failure of beta-secretase 1 inhibitors to show efficacy, it is important to reconsider what the real barriers to progress in this field are and identify emerging opportunities. It is intended that this analysis should inform the development of a strategic action plan that will contribute to the G8 ambition of delivering a disease-modifying treatment for dementia by 2025, and support progress towards and beyond this goal [3].

2. Background

In December 2013 the UK government hosted the G8 Dementia Summit to enable the members of the constituent countries to discuss and formulate an international approach to the global challenge of dementia [5]. The G8 stated that dementia research should be made a global priority with a key aim of developing a cure or disease-modifying therapy by 2025 [3, 5]. During the Summit, it was also agreed that dementia research was under resourced and funded [5]; this has subsequently led to the establishment of a number of important research initiatives aimed at addressing this specific challenge [6-10]. For example in the UK, in 2015, the UK Government published the 'Challenge on Dementia 2020', an iteration of the 2012 Dementia Challenge, outlining the government's aims to improve dementia care, support and research by 2020 [6]. To meet this challenge in the UK the Medical Research Council (MRC), part of UK Research and Innovation, founded the Dementias Platform UK (DPUK) [7] in 2014 with £50 million support for coordinated data and clinical research infrastructures and experimental medicine collaborations with industry. The Dementia Discovery Fund [8] was established in 2015 as a global venture capital fund with the aim of investing in new and emerging disease-modifying therapeutic approaches and facilitating the progression of potential new drug targets through to early clinical development and testing. Also in 2015, the Drug Discovery Alliance (DDA) [9] was launched by Alzheimer's Research UK (ARUK), bringing together three institutes (University of Cambridge, University of Oxford and University College London) with the aim of bridging the gap between discovery science and drug development. In addition, the UK Dementia Research Institute (UK DRI) [10] was founded in 2016, comprising six centres within universities across the UK, with £290 million of co-funding from the MRC, ARUK and the Alzheimer's Society.

Together, the DDA, DPUK and UK DRI aim to transform the treatment, care, prevention and diagnosis of dementia, through coordinated discovery science and translation to people living with dementia.

Despite these and other efforts, significant gaps still exist that hamper the development of disease-modifying treatments for dementias. To address these gaps, ARUK convened a panel of experts in the dementia field, including global academic and industry researchers, to identify and prioritise key thematic areas that are not the current focus of research and funding initiatives in this field. During 15 and 16 May 2018 the panel met in London, UK to discuss how to tackle each specific gap and develop an action plan around each theme. The action plan was intended to be future looking, to provide important information to facilitate the progress of dementia research and ultimately inform and direct the development of life-changing treatments for dementia.

The meeting was organised around six themes: (1) translating genetic risk factors into biological processes; (2) better understanding neuronal resilience to inform novel drug targets; (3) facilitating robust and reproducible drug target validation; (4) identifying appropriate populations of appropriate subjects for Phase IIa proof-of-concept clinical trials; (5) improving approaches to assess drug-target engagement in humans; and (6) innovative approaches to conducting clinical trials if we are able to detect dementia diseases 10-15 years earlier than we are able to today. Each theme will be reviewed in this paper and the key recommendations are outlined. We also include a preliminary action plan to attempt to begin to address and resolve these recommendations.

3. Translating genetic risk factors into biological processes

Understanding genetic vulnerability and its impact on neuronal health and biology

Important advances have been made in identifying genetic factors that contribute to the risk of developing diseases that may cause dementia, and particularly AD. Mutations in amyloid precursor protein and presenilin 1 and 2 cause autosomal dominant AD, and the apolipoprotein E (*APO E*) ε4 allele is a major risk-factor for late onset AD [11]. A key goal of current AD research is to seek out

novel disease-risk genes, elucidate their biological function in the development of the disease and try to interpret important gene-gene or gene-environment interactions with the aim of identifying novel approaches to the treatment and prevention of AD and other neurodegenerative diseases. The standard method for identifying disease-risk genes has been genome-wide association studies (GWAS), and this approach has led to the identification of (at least) an additional 21 genetic risk loci [12]. However, these are highly complex diseases likely caused by the composite action of multiple disease-related genes. This compounds the challenge of translating genetic findings into functional mechanisms that are important in disease pathogenesis [12] and consequently, valid targets for the development of effective therapeutics. Discussions in this session focussed on approaches to improve the translation of genetic findings into disease biology using a more integrated biology approach, better tools and analysis of genotype-phenotype correlations to provide a more comprehensive understanding of disease causation and inform future therapeutic drug discovery and biomarkers.

As many genetic factors having been identified as contributing to the risk for developing AD, the research focus has shifted from identifying novel risk factors toward understanding how such risk factors lead to changes in biological processes and pathways, some of which are already known to be affected in dementing and other neurodegenerative diseases. Moving from genetic data to a potential therapeutic will involve different tools and areas of expertise, including *in silico* and laboratory approaches to structural biology, cell biology, and pharmacology. Leveraging emerging technologies (such as single cell studies or induced pluripotent stem cell models) will also enable acceleration of the investigation of the links between genetic data and potential therapeutics. The Open Targets partnership is a good example of this approach [13]. It brings together expertise from six different institutions and uses human genetics and genomics data to systematically identify and prioritise drug targets for therapeutic development [13]. Another good example is seen in schizophrenia research, where understanding the role of the complement component 4 locus involved the application of different tools and datasets (including GWAS and expression data from

post-mortem brains), and genetic engineering of animal models to understand the biological mechanism [14]. This approach identified potential biological targets from genetic data that may result in the development of novel therapeutics. These examples of partnerships and collaborations, and application of different tools, should be more widely adopted by the dementia research community to bridge the gap between genetic signals to biologically relevant therapeutic targets. Interdisciplinarity and development/application of a broad range of tools and technologies are also at the heart of the UK DRI research network, aiming to accelerate our mechanistic understanding of dementia to find new ways to prevent, diagnose and treat dementia effectively [10].

A significant challenge in translating genetic data into biological processes is the lack of understanding of the underlying role of individual genes, and how they relate to disease progression and phenotype in later life. Genomic analysis across the natural history of the disease would enable a better understanding of the genes involved at different stages of disease, provide additional insight into the disease mechanism(s) and inform the development of alternative interventions or new areas of research. Part of this genetic analysis should also include identification of the genetic influences on rate of disease progression. This could be approached by capitalising on longitudinally phenotyped cohorts that include and contrast subjects with sporadic AD to analyse the genotype-phenotype interactions and progression of the disease.

To support these approaches, it will be important to identify key expertise from different disciplines that are currently missing from dementia research and proactively engage with subject matter experts from diverse areas such as data science, not only to bring that expertise into the dementia field but also to promote the exchange of knowledge and innovation. Barriers to collaborative and interdisciplinary research also need to be understood and addressed. For example, intra-institutional collaborations may have been hindered in the UK by the fact that a publication could only be submitted once to the former Research Excellence Framework assessments from each institution [15]. The evaluation of collaborative research outputs has changed, with a greater emphasis on

impact and contribution, but further changes in the evaluation and recognition process are needed if we are to foster true collaborative efforts.

There is also a need to bring together experts from other relevant disease and basic science areas of expertise, particularly those shown to have an increasingly important role in dementia research (e.g. immunologists and lipid biologists), and to encourage intra- and interdisciplinary collaboration. This approach has been successful in Huntington's disease research, where the CHDI Foundation (https://chdifoundation.org/) manages a network of over 600 researchers worldwide, facilitating the sharing of ideas and information that encourages active collaboration. A similar model could be adopted for dementia research. Dementia symposia and workshop sessions could be included in conferences hosted by other disciplines, such as immunology and oncology. Similarly, subject matter experts in relevant fields could chair these symposia or workshops (e.g. asking immunologists to lead neuroinflammation discussions). Such approaches would encourage cross-discipline fertilisation and potentially bring new expertise into the dementia field.

This approach has been adopted by the DPUK for experimental medicine working groups, and the Wellcome Trust Consortium for the Neuroimmunology of Mood Disorders and Alzheimer's Disease (NIMA) [16]. The NIMA Consortium is investigating novel therapeutic and biomarker approaches for neurodegeneration based on the biological links between inflammation and neurodegeneration and a number of clinical compounds derived from immunology drug discovery. To address this challenge, the Consortium assembled a team of academic and industry scientists with diverse expertise in imaging, animal models, clinical phenotyping and informatics. Such collaborative and interdisciplinary approaches could facilitate the translation of genetic research that impacts on cell biology into neurodegenerative research and development.

Summary of recommendations and suggested actions

3.1.1. Facilitate translation of genetic risk factors into targetable biological processes and pathways using a more integrated biology approach

3.1.2. Support the application of tools and expertise from other fields to better translate genetic information into cell biology and drug development

3.1.3. Encourage research that seeks to carry out genomic analysis along disease progression to identify the genes involved at different stages of disease

3.1.4. Support interdisciplinary collaboration, and the development of dementia symposia and workshop sessions in other relevant disciplines to foster cross-fertilisation of ideas and bring new expertise into the dementia field.

4. Better understanding selective neuronal vulnerability and resilience to inform novel drug targets

Could a better understanding of why some neurones die and others are resistant to cell death identify novel drug targets?

This session was focused on why some neuronal cell populations die very early in the course of the disease, others die at a later stage and still others do not seem to degenerate at all, and whether understanding this difference could help identifying novel targets for drug development. Recent research has identified multiple neurodegenerative pathways that result in a domino-like cascade of events that eventually lead to the development of dementias. However, these changes are not seen in all cases of AD [17, 18]. The characteristic features of AD are the pathological accumulation of extracellular plaques composed of amyloid-β protein and intraneuronal tangles consisting of altered forms of tau [17]. A long-standing puzzle in AD research has been the finding that there may be a substantial number of Aβ plaques in the brain of some individuals who have otherwise normal cognition and conversely people who exhibit phenotypic AD but have little or no plaque or tangle

deposition [19, 20] Studies show that Aβ deposition is an early event that may play a harmful role in the development of AD, however, the mechanisms that link Aβ to neurodegeneration are poorly understood. Moreover, intermediate Aβ species (e.g. oligomers) perhaps contribute more to nerve injury than to plaques [21]. Clinically relevant symptoms tend to emerge around the same time that tau pathology is correlated with cell death, although it is also acknowledged that the intermediate oligomeric species may play a critical role in such developments [22]. Moreover, some brain regions (hippocampus, amygdala and cerebral cortex) appear to show a selective vulnerability to plaque accumulation and tau associated neurodegeneration, while others (basal ganglia, cerebellum, brain stem and spinal cord) are initially spared [23, 24].

These observations suggest that understanding why some brain structures are more vulnerable to insults than others could be gained by examining the molecular differences between neurones that are susceptible to neurodegeneration and those that are relatively protected. For example, excitatory but not inhibitory neurons, that differ in their expression of proteins that enable protein degradation, accumulate damaging tau aggregates in a genetically engineered mouse model of tau pathology spread [25]. This type of approach may aid the identification of novel disease mechanisms that could be exploited to develop alternative therapeutic targets for disease management with a potentially higher success rate for treatment. For example, recent studies have explored the locus coeruleus, a brainstem nucleus in the central nervous system (CNS) that is the primary site for production of noradrenaline and has diffuse noradrenergic innervation. Noradrenergic neurons in this region play a central role in normal cognitive function, and so loss of innervation in this region is postulated to be linked to cognitive decline, suggesting that noradrenaline signalling in the CNS might be a viable therapeutic target [26].

The key advance enabling this approach was the possibility of biologically mapping the molecular signature of different neuronal populations in healthy brains versus brains from subjects with neurodegenerative diseases. This may lead to a better understanding of the biological processes

associated with neuronal vulnerability and may allow for a spatial and chronological characterisation of the neural cell systems affected in dementia. The Allen Institute is making progress in this area, with a project entitled Aging, Dementia and Traumatic Brain Injury Study [27] within the Allen Brain Atlas [28]. It would be very useful to explore and expand the potential of these projects by integrating data from different research groups globally. This requires overcoming barriers to data sharing, data accessibility and integrative approaches across institutions to enable interconnection/interoperability and linkage of datasets. A complementary approach to mapping neuronal vulnerability has also been suggested at the National Institute of Health AD Summit 2018 [29] to develop an AD connectivity map based on 'omics' expression signatures in disease-relevant cell types. Further investigation using an omics-based approach could systematically map resilience and vulnerability by brain region as well as tracking the trajectory of the disease [30]. Integrating multiple sets of omics data using computational and statistical tools can be used to analyse the molecular pathways in specific brain regions and perhaps identify the more vulnerable pathways. Others have suggested that additional approaches are needed, such as a more active investigation of glia and vascular changes [31].

This could be studied using longitudinal structural magnetic resonance imaging (MRI) or synapse positron-emission tomography (PET) imaging, however another important aspect is the evaluation of post-mortem or resected human tissue, something that is not necessarily straightforward to obtain from well characterised cases and without significant post-mortem delay, required for high-quality samples. It was proposed that researchers need better access to living tissue from people living with dementia, and the panel recommended that this be achieved by enabling access to resected tissue from surgeries and utilising excess biopsy tissue. One approach suggested to streamline access was through the UK Brain Banks Network, a coordinated national network of UK brain tissue resources for research purposes [32]. It would be important for neurosurgeons to follow a standard operating procedure (SOP) in order to facilitate the collection of high-quality tissue for the brain banks and so it was proposed to develop SOPs in collaboration with the MRC Brain Bank Initiative and to identify

best practice globally. It was also suggested that the Brain Bank Steering Committee engage with cohort principal investigators to encourage them to obtain consent for the use of brain tissue for research purposes. Other suggestions included encouraging pre-consenting for people living with dementia in clinical trials for post-mortem brain donation, collaborating more closely with neurosurgeons, and standardising brain tissue processing in order to maintain its usefulness for study (e.g. rapid cooling of excised brain tissue).

Finally, dementia research organisations can set the agenda, drive research and encourage collaboration by sharing of information with the wider research community [33]. Pre-clinical biological data can often be difficult to disseminate in an accessible format, due to the unstructured nature of certain data sets, for example omics type data and imaging. Developing solutions for data sharing and accessibility may enable the field to progress at a faster rate.

Summary of recommendations and suggested actions

4.1 Use an omics-based approach, and others such as imaging, to map resilience and vulnerability by brain region including all cell types to better understand disease processes, characterise disease trajectory, and potentially yield novel targets for drug discovery

4.2 Access to tissue

4.2.1 Generate neurosurgical SOPs to enable research access to excess biopsy tissue and resected tissue from neurosurgery, where undertaken for clinical indications

4.2.2 Encourage pre-consenting for those in trials for post-mortem brain donation and ensure procedures are in place to optimise this process (e.g. enforce procedures to ensure rapid brain cooling at time of death).

5. Robust and reproducible target validation

The need to improve validation of potential drug targets

Currently only symptomatic treatments for dementia are available. At best, they transiently provide limited cognitive benefit in approximately 40% of people living with dementia, and they have no impact on the underlying disease processes or the rate of cognitive decline [3, 4]. While development of symptomatic treatments has slowed, the search for dementia preventing or modifying treatments has increased significantly [34].

A plethora of innovative approaches to drug discovery are emerging, with the identification of putative novel mechanisms and potential drug targets being published in high profile journals. However, robust and reproducible biological validation of potential new molecular targets is key to successful and productive drug discovery. It is critical that exciting early published findings can be reproduced across different model systems and laboratories to provide confidence when moving from laboratory to clinic. However, translating these early novel biology findings into robust drug target validation is often met with failure and there are still many significant barriers to successful drug development. The reasons for this are many fold, including incentives to publish pre-clinical work without the necessary robust evidence for relevance of applicability to human disease; fundamental differences in the biology and degeneration of brain cells in different species; and limitations in the human disease models and outcomes. Incentives to publish novel findings as rapidly as possible detracts from reproducing initial novel findings either within the same academic lab or in independent labs. Grant funding does not always readily allow the reproduction of findings in different *in vitro* and *in vivo* models, and validation data are less attractive to publishers. In addition, the pressure on both academic and biotech researchers to progress targets rapidly to the next stage of development does not necessarily support robustness or establishing cross-species homologies. Whilst these issues are not confined to dementia research, the current paradigm for target validation in neurodegenerative research should be strengthened significantly with an

emphasis on both robustness and reproducibility of early preclinical experimental methodology and findings.

Significant effort is required to address these issues with emphasis on training and awareness (e.g. scientists trained in pharmacology and rigorous experimental design including robust statistics). High quality collaborative and interdisciplinary proposals should be incentivised, to encourage research groups working on identical/similar targets can share their expertise, minimise risk and cost and improve robustness and reproducibility through integration of diverse disciplines. There was also consensus that incentivising validation of potential drug targets through cross verification from two or more sources, for example bioinformatics data, genetics, cell biology *in vitro* and *in vivo* and real-world observational data would result in significant long-term benefits.

The results of an interesting discussion on facilitating reproducibility and robustness of early experimental findings focussed on the expertise of independent grant review. It was proposed that high quality grant review could be achieved by the following: (1) encouraging wider expertise from other fields to participate in the grant peer review process; (2) provide detailed and constructive feedback, which can help researchers better understand how to achieve robust target validation; and (3) use of good practice guidelines that can be shared across the scientific community. Examples of good practice methodology could be collated in order to develop the guidelines for drug target validation similar to the Animal Research Reporting *In Vivo* Experiments (ARRIVE) guidelines [35] or the Organization for Human Brain Mapping's Committee on Best Practice in Data Analysis and Sharing [36].

Incentives to researchers have not always supported robustness and reproducibility of data, where tenure and promotion structures have placed great emphasis on novel, high impact research, which may have high impact, but risks unreproducible outputs based on a limited number of experiments. Therefore, the incentive structure and training should be reconfigured to also promote validation of results. It is important to raise awareness and incentivise drug target validation and translation as a

348 critical process of drug development for example, encouraging researchers to conduct experiments
349 that provide predefined 'NoGo' decision endpoints in a research proposal, effectively rewarding the
350 termination of futile lines of enquiry. These proposals could be adopted readily and included in the
351 guidelines for grant applications and could be an additional criterion for review.

352 Wider dissemination of information on ineffective technologies/techniques and publishing of
353 negative results should also be supported. This could be achieved through funders encouraging open
354 research platforms (e.g. AMRC Open Research https://amrcopenresearch.org/, Wellcome Trust
355 Open Research https://wellcome.ac.uk/what-we-do/our-work/open-research, and Alzforum
356 https://www.alzforum.org/) to publish data that might otherwise not be published by peer reviewed
357 journals (e.g. negative data). This would enable more timely 'Go'/'NoGo' decisions to be made, and
358 streamline the translational pipeline.

359 The drug target validation process is at the interface between academia and industry, and promoting
360 better collaboration between the two can lead to a better understanding of the basic science of AD
361 and the requirements for drug development. This will ultimately improve and enhance the validation
362 of novel biological findings. Progress in this area has been made through initiatives such as ARUK's
363 Drug Discovery Alliance and Dementia Consortium [37], as well as the US initiative Accelerating
364 Medicines Partnership - Alzheimer's Disease (AMP-AD) [38], although more needs to be done to
365 expand this and other collaboration models to additional institutions and countries.

366 The translation of laboratory-based findings to clinically relevant therapies is very complex. Pre-
367 clinical testing of potential new therapies for AD and other neurodegenerative disorders relies on
368 effective animal models of disease or disease mechanisms that have both face and construct validity.
369 Whilst all animal models have their limitations, a number of established and accepted
370 pharmacodynamic animal models, based on familial mutations in AD, are now used widely to
371 support dementia research. However, even with these select number of models, there is extensive
372 variability in the design of animal experiments between different research groups. This results in

animal models with varying characteristics, which ultimately leads to lack of consistent validation. Compounding the issue, is the lab variability introduced by not using the appropriate background or control strains. To improve validation, optimised experimental design protocols for animal models in dementia should be developed and standardised. This should entail an in depth review of existing models and experimental procedures followed by open publication of standardised animal protocols and promotion of their use (e.g. preference setting by high profile journals and funding bodies), similar to the NEWMEDS initiative for schizophrenia research [39]. Scientists working in osteoarthritis research have recently published 'considerations for the design and execution of protocols for animal research and treatment' [40] to complement the ARRIVE guidelines [35], and a guide has also been produced for Huntington's disease animal models [41]. A similar protocol could be developed and adopted for animal model research in dementia diseases.

Summary of recommendations and suggested actions

5.1.1 Provide training for scientists in areas of skills gaps (e.g. pharmacology, statistics) and facilitate collaboration

5.1.2 Incentivise validation of potential drug targets through cross-verification with different sources of data and different experimental systems

5.1.2.1 Funders should require robust validation approaches in funding applications, with use of multiple data sources/systems and, where appropriate, use of independent labs

5.1.3 Support the sharing of information on ineffective technologies/techniques and publishing of negative results

5.1.3.1 Funders should encourage open research platforms (such as Alzforum) to publish negative data and the scenarios within which they are tested

5.1.4 Facilitate translation from novel target validation to early drug discovery (e.g. through models such as the ARUK Dementia Consortium, where expert scientists from different sectors work together)

5.1.5 Develop an optimised experimental design protocol for animal model research

5.1.5.1 Review experimental design and methodologies and publicise and encourage use of suggested standardised protocols.

6. Appropriate choice of subject populations for proof-of-concept clinical trials

Who to select for early proof-of-concept clinical trials

Between 2002 and 2012, only one compound of 244 evaluated in clinical trials for AD reached the market, translating to an overall attrition rate of 99.6% with 98% of those evaluated in Phase III clinical trials failing to show efficacy [42]. The number of compounds that progress to regulatory review is among the lowest for any therapeutic area [42]. One of the factors often linked to this high failure rate is inappropriate selection of subject populations in early clinical trials, leading to results that fail to translate through to Phase III trials. A key aim of Phase Ib/IIa studies is to show proof of pharmacology over a short period of time, and these trials typically restrict inclusion to a very small fraction of the total pool of people living with dementia (e.g. excluding by common co-morbidities, or narrow stage of disease). Thus, the typical Phase IIa population of people living with dementia may not be representative of the wider cohort that is the likely population to be evaluated in Phase III. For AD it may be beneficial to consider using a more heterogeneous population in Phase IIb trials, to increase the probability of success in the wider patient populations or to restrict recruitment in Phase III trials to a population of patients more likely to benefit from a particular treatment.

The current challenge of recruiting appropriate subjects to proof-of-concept clinical trials is complex given the questions that need to be addressed by early stage studies, i.e. safety and proof of mechanism/efficacy on disease progression within a relatively short period of time. For evaluation of an AD therapeutic prodromal AD and/or early AD may not be the relevant populations, as the time

taken to show a clear change in cognitive decline is likely to be beyond the reasonable duration of such trials (typically over 18 months), until a time when there is a consensus on more sensitive endpoints. Therefore, in order to effectively demonstrate proof of concept, alternative subject populations could be recruited to these studies, with subsequent studies expanding to include the AD populations. This strategy relies on the true relevance or functional equivalence of the alternative population to AD. Such equivalence is often assumed, but rarely proven. For example, targeting clearly defined populations such as Down's syndrome or familial AD to demonstrate mechanistic efficacy could not only facilitate therapeutic proof of concept but also enable the development of treatments for populations with significant unmet medical need. If proof of concept were to be demonstrated in these groups, trials could then be expanded to incorporate the wider AD population. In both the Down's syndrome and familial AD populations, Aβ and tau pathology plus the onset of cognitive impairment follows a path similar to that in sporadic AD, but in both populations the onset and progression of the disease is more predictable and homogeneous with less co-morbidity than late onset populations [43, 44].

The aims for research and development in recruiting people with Down's syndrome, familial AD, and sporadic AD to a study somewhat differ. People with Down's syndrome represent a population in which to explore the early efficacy of drugs, particularly those targeted against Aβ and tau, which slow down disease progression. Almost all people with Down's syndrome progress to AD and dementia, with an Aβ pathology which is very similar to that observed in people with AD [43]. Thus, they represent a population of huge unmet medical need in their own right. In addition, they arguably represent a more homogeneous population where the Aβ pathology is well defined and where drugs can be evaluated for pharmacodynamic effects and early efficacy at a very early stage in the disease process. The latter is also arguably the case for familial AD. However, one important consideration is that both these populations are different to the majority of people with sporadic or late onset AD: they are younger, more commonly present with phenotypes other than typical amnestic mild cognitive impairment AD and have subtly different neuropathology to sporadic AD

and differences in the role of vascular pathology in pathogenesis. In addition, in people with Down's syndrome, the variability in pre-morbid cognitive function raises challenges for outcome measures and informed consent issues, which is not the case in familial AD. These and other differences may compromise the predictability of a drug effect, given the non-equivalence to most people with AD. Even taking this into account, these populations may offer a route to delivering early proof of efficacy for some compounds and should be considered on a case-by-case basis depending on the mechanism of treatment.

Alongside this approach, new strategies should be explored to better stratify subjects into clinical trials. There is a requirement to identify, recruit, characterise and allocate people using clinical study registers to create dementia cohorts. One potential solution is using longitudinal phenotyped clinical registries and readiness cohorts, the current strategy of the DPUK (which includes the Deep and Frequent Phenotyping study) and European Prevention of Alzheimer's Dementia (EPAD) Consortium respectively [45, 46]. Furthermore, there is currently very little information on genetic factors linked to the rate of disease progression, or phenotypic variance (e.g. amnestic vs. posterior cortical atrophy vs. logopenic aphasia variants of AD). Large scale and long-term registers allow for people to be profiled mechanistically and longitudinally, including disease progression, to distinguish genetic and environmental determinants of fast versus slow progressors, enabling more accurate stratification for clinical trials. This approach has been informative in Parkinson's disease and frontotemporal dementia [47, 48].

Recruitment of individuals to clinical trials remains low even with the existence of many cohorts and the above-mentioned registries. In order to improve recruitment to clinical trials, it is important to understand the barriers and incentives to increase clinical trial participation and to engage with principal investigators to incentivise the use of cohorts. This is one of the priority areas promoted by Bill Gates in his plans for investment in AD [49]. One barrier to increasing clinical trial participation by well characterised subjects within existing cohorts is the mutual exclusivity between longitudinal

observational phenotyping over several years and therapeutic studies; these activities do not need to be mutually exclusive, but in practice they often are. To address this issue, it is essential that participation in research is increased so that both types of studies can coexist without mutual exclusion.

6.1. Summary of recommendations and suggested actions

6.1.1. Select relevant populations which best address the questions being asked at the relevant stage of development i.e. proof of concept/mechanism/pharmacology

6.1.1.1. Focus on mechanism/pharmacology/efficacy in clearly defined populations initially to allow demonstration of proof of mechanism/pharmacology and subsequently expand to the wider AD population if appropriate

6.1.1.2. Examples of such populations could be Down's syndrome or familial AD, where there are huge unmet medical needs, and pathology is sufficiently similar to that of sporadic AD, but disease progression is more rapid or more predictable

6.1.1.3. Early proof of concept populations could provide the predictive data required to expedite the next phases of clinical development

6.1.2. Consider how to improve genotype-phenotype translation to enable stratification of people living with dementia for clinical trials

6.1.2.1. A longitudinally phenotyped experimental medicine register could facilitate this

6.1.2.2. Profile people living with dementia mechanistically and longitudinally along disease progression to better understand the biology/pathology associated with fast and slow progressors to enable accurate stratification

6.1.3. Understand barriers and incentives to increasing clinical trial participation and incentivise the use of cohorts and registries

6.1.3.1. Longitudinal observational phenotyped cohorts and therapeutic readiness cohorts are often mutually exclusive but are equally critical for clinical research - increase participation in research to fill both cohorts.

7. Improving approaches to assess drug-target engagement in humans

Making more informed decisions in clinical development

Prior to neurodegenerative disease therapeutics entering the clinical pipeline they are screened for their pharmacology, pharmacodynamics, pharmacokinetics and toxicity in preclinical model systems. Data from these studies are intended to inform factors such as safety, optimal clinical dose range, blood-brain barrier penetration and binding to the intended target [50]. Although these preclinical data are informative they do not fully describe all the clinical findings in early human trials. It is therefore important to be able to make more informed 'Go'/'NoGo' decisions early in clinical development and establish approaches to minimise risk and maximise the potential for success as a therapy progresses through the various stages of clinical development [50].

Demonstrating proof of target engagement/pharmacology in humans early in clinical development is crucial for reducing the risk involved in progressing novel drug therapeutics from Phase I safety/pharmacokinetic studies to later stage efficacy studies. In other fields, such as psychiatry, ascertaining the clinical pharmacology profile of novel drugs in early clinical development is a relatively common practise (e.g. PET ligand displacement studies) but is often overlooked in neurology therapeutics development, often due to lack of appropriate tools in clinical practice. Instead, compounds are progressed directly from Phase I/Ib safety/tolerability studies into Phase IIb/III efficacy studies. This strategy, particularly used in the narrow focus of the development of therapeutic antibodies, can contribute to poor decision making along the path of dementia drug development and testing leading to unsatisfactory outcomes in costly, late stage clinical trials.

If achievable, being able to show drug target engagement and pharmacological consequence at the site of action serves a number of useful purposes: (1) it establishes that the therapeutic reaches and

engages the relevant target site of action; (2) determines the relevant pharmacological dose range for moving to later stage clinical trials; (3) it significantly reduces the risk of progressing a drug inappropriately into late stage development; (4) it allows optimisation of dosing regimen based on established pharmacokinetic/pharmacodynamic relationships; and (5) it provides confidence that the mechanistic hypothesis, being targeted by the therapeutic, is truly being evaluated for efficacy in a population of people living with dementia. However, due to the costs associated with this early stage of development (particularly if new tools / approaches are needed) and a need for more rapid therapeutic development, there may be the potential to bypass these studies. Thus, it is important to find more collaborative risk and cost sharing approaches to show target engagement and drug pharmacology as these studies are critical in early drug development. To date, disease-modifying drugs that have reached Phase III clinical trials are primarily either small molecules or immunotherapies that target Aβ [34]. Behind this wave of Aβ targeted drugs are those that are directed towards tau [34] including those which reduce tau hyperphosphorylation, tau accumulation or prevent the spread of toxic tau species. The current methodologies that demonstrate target engagement for tau are limited to cerebrospinal fluid (CSF) biomarker measurements, because of current uncertainty over off-target binding of PET ligands, even if heuristically binding of these ligands highly correlates with disease pathology and phenotype [51]. More recently, there has been a focus on targeting various neuro-inflammation pathways and processes. It is important, therefore, to establish methodologies for measuring target engagement or proof of pharmacology across a range of these drug target classes, to facilitate a risk-reduced progression of such drugs to the next stage of development.

A second area that is gathering momentum is the measurement of synaptic integrity and health, this can potentially provide a pharmacodynamic endpoint for many different therapeutic approaches, and also has the potential to serve as a relevant diagnostic biomarker. Relevant methodologies include PET approaches for measuring synaptic density, and magnetoencephalography to measure circuit function including changes in oscillations [52]. One example of such an approach is the

synaptic vesicle glycoprotein 2A (SV2A) PET ligand (radioligand [53] (UCB-J) which is currently being evaluated as means of quantifying synaptic density. This radioligand ligand has been validated in humans including people with AD [53]. Initial studies suggest this approach may not only provide evidence of target engagement and early proof of mechanistic concept but could provide an approach to assessing prognostic drug efficacy as well as potentially being useful as a diagnostic for neurodegenerative diseases more generally.

The discussions in this session focused on how to scope and facilitate collaboration in developing cost- and risk-sharing approaches to demonstrate target engagement, drug pharmacology and pharmacodynamic effects for target class mechanisms e.g. tau or neuroinflammation. This would span different drug approaches across multiple companies/partners. A potential approach is to establish public-private partnerships, similar to the DPUK's Synaptic Health Theme, and the model used by ARUK's Dementia Consortium for early drug discovery projects [7, 37]. The Consortium aims, through a cost-sharing and risk-sharing approach to translate fundamental academic research to early drug discovery programmes for new dementia treatment [37].

Regarding the exploration of new methodologies for measuring target-engagement and proof of pharmacology, one area that is underdeveloped in the UK is the sampling of CSF for relevant pharmacological endpoints. CSF is a useful resource in AD, given the breadth of analysis now available, for determining drug pharmacodynamic effects, pharmacology and target engagement as well as assessment of disease biomarkers, tracking disease progression and potentially improving early diagnosis [54]. However, unlike some other European countries, lumbar punctures are less commonly used in dementia clinical practice and dementia research. CSF sampling has recently been included in the updated National Institute of Care Excellence dementia guidelines, also showing the importance of this resource in a clinical setting [55]. Potential solutions to this issue would be to raise awareness of the high tolerability as well as utility of lumbar puncture, within both healthcare providers and the general public. However, it was noted that to achieve success in this area in the

UK, it is necessary to understand how to change the culture and training for CSF collections to become a routine procedure.

The UK is a major partner in the international development of other new technologies for dementia research, including multiple UK centres participation in the EU Joint Programme - Neurodegenerative Disease Research (JPND) 2016-17 initiative for standardisation and harmonisation of new methods including magnetoencephalography, tau-PET, and ultrahigh field MRI [56]. UK and international support for these initiatives has succeeded in bringing expertise in to dementia research which had not previously been engaged.

Summary of recommendations and suggested actions

7.1.1. To scope and facilitate collaboration in developing cost- and risk-sharing approaches to demonstrate target engagement, proof of mechanism and proof of drug pharmacology for drug mechanisms common across multiple companies/partners

7.1.1.1. Public-private partnership approach, similar to the cost-sharing, risk-sharing approach set-up for ARUK's Dementia Consortium and DPUK

7.1.1.2. To focus on common mechanisms for drugs currently in late stage preclinical development

7.1.2. Facilitate the use of CSF sampling to determine target engagement, proof of drug mechanism and effects on pharmacodynamic endpoints

7.1.2.1. Understand how to change the culture, improve training, and encourage CSF collections to become a routine procedure

7.1.3. Support advances in translating putative pharmacodynamic endpoints into useful clinical assays.

8. Innovative approaches to conducting clinical trials if we are able to detect diseases 10-15 years earlier than we do today

How to approach clinical trials differently if detection/diagnosis is achieved earlier

The majority of potential AD therapeutics have failed to show efficacy in Phase III clinical trials. At the time of writing, there have been no new drug approvals for treating AD since 2003. A potential reason for lack of efficacious and novel therapeutics in late stage clinical trials is that treatment intervention may be occurring at too late a stage in the disease process. There is widespread agreement amongst experts that if we were able to detect, and ultimately diagnose, disease at a much earlier stage then the chance of successful disease-modification, in addition to symptomatic therapies, would increase significantly. To this end, researchers are looking towards developing tools that will allow early detection, diagnosis and treatment of diseases underpinning dementia at an early stage of disease. As a minimum these tools could help to efficiently and accurately triage at-risk individuals for detailed clinical diagnosis but ideally, they would provide a tool that detects and subsequently diagnoses early stage disease, where perturbation of the disease process itself pharmacologically would have the greatest long-term therapeutic benefit.

Several hurdles need to be overcome if such detection/diagnostic tools do become available, not least that the duration of Phase IIb/III clinical trials will increase significantly to allow measurement of clinical efficacy of drugs. Already, with the disease-modifying drugs currently in development, it is a challenge to conduct trials of sufficient duration to demonstrate a difference in the slope of cognitive decline. Early detection/diagnosis will compound this issue if existing cognitive outcomes retain primacy as measures of a beneficial effect, as trials will be required to run for even longer periods. If we are able to reliably detect/diagnose 10-15 years earlier, innovative approaches to how late stage clinical trials are conducted and implemented will be necessary which may include novel cognitive outcome measures more sensitive to neurodegenerative changes at their earliest phase [57]. Regulatory bodies are looking to provide conditional approval of dementia drugs based on

surrogate markers which may enable alternative means of collecting Phase III clinical trial data in a 'real-world' setting utilising memory and brain health clinics for data collection [58]. This would allow for passive and active monitoring remotely using standard clinical endpoints but also digital approaches, generating 'real-world' data. To address this, a community-based trial protocol is currently being developed by ARUK to provide an exemplar of conducting real world (e.g. memory clinic-based) pivotal clinical trials for AD ('virtual' clinical trial). To achieve this, there needs to be increased engagement with regulators to inform guideline development and regulators need to be persuaded of the value of a virtual clinical trials approach.

An alternative and complimentary strategy is to develop more sensitive tools for detecting cognitive change that can be used at-scale. Many outcome measures use well established technologies that have been developed for use specifically in a clinical context. These measures are unsuitable for use in large pre-clinical populations. A strong case can be made for a new generation of digital cognitive phenotyping tools that can detect early changes indicating increased clinical risk. This is an opportunity for stakeholders to collaborate in developing standard tools that are understood and accepted by regulators, industry, and academia.

If it is possible to detect AD much earlier than current methods allow, an important factor to consider is the impact for individuals who have the disease detected and their families. Current trials use different outcome measures (clinical, functional and biological) to determine the efficacy of the treatment, however these outcomes have not been determined patients and their carers but are instead an objective measure of clinical symptoms. Therefore, it will be extremely important to understand the preferred outcomes of people living with dementia for early stages of disease, which can then inform drug development and provide additional endpoints for clinical trials. To this aim, ARUK has begun to explore an outcomes project in collaboration with researchers, people affected by dementia, clinicians, and regulators [59]. It is important to continue supporting projects to understand the outcomes people living with dementia prefer and persuade both the research

community and regulators of the importance of these in informing clinical trial design and conduct. The AD community are not alone in facing these issues. The EU JPND supported a cross-disciplinary working group, the Presymptomatic Neurodegeneration Initiative, where researchers, funders and regulators considered analogous challenges in AD, frontotemporal dementia, motor neuron disease, Huntington's disease and other conditions [60].

Conducting longer clinical trials will also have implications for data protection regulation. Innovators have patent protection as well as data exclusivity for several years, however, with treatments shifting to earlier stages of the disease and the possibility that patents may not survive for many years after drug approval due to longer clinical trials, there may be a need to evolve data protection regulation and patent life in line with developments in approaches to treatment.

Summary of recommendations and suggested actions

8.1.1. If we detect neurodegenerative diseases 10-15 years earlier, propose and theoretically validate a new approach for conducting and implementing late stage, pivotal clinical trials

8.1.1.1. Develop a community-based trial protocol to provide an exemplar of conducting a real world (e.g. memory clinic) pivotal clinical trial for AD

8.1.1.2. Engage with regulators and relevant bodies to inform the development of an innovative approach to the conduct of late stage clinical trials including digital cognitive phenotyping strategies

8.1.1.3. Educate regulators regarding the value of a 'virtual' clinical trials approach

8.1.2. Understand outcomes people living with dementia prefer for early stages of disease, which can inform drug development and provide additional endpoints for clinical trials

8.1.3. Work with relevant stakeholders to evolve data protection regulations in line with the shift to treating earlier in the disease course.

9. Conclusions

The national and global objective of delivering a disease-modifying treatment for dementia by 2025, as well as the development of improved symptomatic therapies, will require a multi-faceted approach to broaden current research areas by addressing prevention, earlier detection/diagnosis, disease mechanisms and the design of clinical trials. Specific recommendations and actions detailed in this paper include:

- Using a more integrated biology approach to translate genetic data into cell biology
- Map resilience and vulnerability by brain region using an 'omics'-based approach
- Include requirements in funding applications for robust target validation in pre-clinical models and humans
- Using multiple data sources to increase reliability and reproducibility of findings
- Focus on demonstrating proof of mechanism/pharmacology/efficacy in clearly defined populations (e.g. Down's syndrome) initially and subsequently expanding to the wider AD population
- Develop cost-and risk-sharing approaches to demonstrate target engagement
- Developing a community-based clinical trial protocol to promote a paradigm shift in how late stage clinical trials could be conducted.

In addition to specific recommendations for individual themes, there were also a number of recommendations that were relevant across all the themes. These include incentivising collaborations both within the dementia field and with other fields, consideration of data sharing, interoperability and centralised databases, promoting and supporting the sharing of research tools, changing the incentives in academia and industry to encourage a more collaborative approach and raising education and awareness of the public, research community and clinicians. The overarching resolution is to find additional ways to incentivise collaboration, particularly interdisciplinary collaboration, to standardise approaches, to re-think clinical approaches to early and late stage

clinical trials and to efficiently and comprehensively share data and samples at all levels across the scientific community. All are essential to accelerate the progress towards the goal of developing an effective treatment for AD by 2025.

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